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(54) Blood compatible polymer mixture

(57) A blood-compatible polymer mixture comprises at least 95 volume % of a base polymer and no greater than 5 volume % of a polymer additive comprising a polymer(dialkylsiloxane) segment chemically bonded to a polyurethane segment, the polymer additive being dispersed throughout the base polymer and being characterized by a γ_c less than that of the base polymer, the polymer mixture being characterized by a γ_c between 10 and 35 dyne/cm.

The base polymer is a good structural polymer, eg polyurethane, whose surface free energy is lowered to convert a surface formed from the polymer from one which is blood incompatible to one which is blood compatible. The polymer mixture may be used to form the blood contacting surface of a biomedical device.

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SPECIFICATION

Blood compatible polymer mixture

One widely accepted hypothesis regarding blood compatibility is that it is maximized within a narrow range of surface free energies which give rise to favorable interactions with plasma proteins. A common measurement of surface free energies is by Zisman's critical surface tension (γ_c). The optimum value has been found empirically to lie within the range of a γ_c equal to about 20 to 30 dyne/cm., see, e.g., R.A. Baeir, Ann. N.Y. Acad. Sci. *17*, 283 (1977).

Common polymers (e.g. polyurethane) which provide the desired physical properties for the blood contact surfaces of biomedical devices often do not fall within this range of critical surface tensions.

Polysiloxanes are known to have a particularly low critical surface tension value and have been suggested for incorporation into polyurethanes to improve the surface characteristics of such materials. However, polysiloxane by itself is known to have a tendency to exude from the polyurethane base polymer as illustrated in Reischl et al., U.S. Patent 3,243,475.

Polysiloxane-polyurethane block copolymers have been suggested for use to modify the surface characteristics of blood contact surfaces of devices of biomedical devices as illustrated in Nyilas U.S. Patent 3,562,352. The technique disclosed for such use includes fabricating the entire blood contact devices from such block copolymers or coating such devices with the copolymers. The block copolymers themselves have poor structural characteristics due to a high proportion of polysiloxane. On the other hand, the coated materials are particularly expensive to form as they are not processable by thermoplastic methods such as injection molding and extrusion. The manufacture of tubing, catheters and other blood-contacting disposable devices from such materials is particularly expensive due to the necessity of employing solution fabrication techniques.

Certain experimental work has been published relating to the blending of block copolymers of polydimethylsiloxane with homopolymers of higher critical surface tensions. These materials are known to produce films with high siloxane surface concentrations. See, for example, D.G. Legrand and R.L. Gaines, Jr., Polym Prepr. *11*, 442 (1970); D.W. Dwight et al., Polym. Prepr. *20*, (1), 702 (1979); and J.J. O'Malley Polym Prepr. *18* (1977). However, all of these references describe the polymer blends in terms of scientific experiments without suggestion that the material would have any advantage for use in any biomedical application.

In a first aspect the present invention provides a blood-compatible polymer mixture comprising at least 95 volume % of a base polymer and no greater than 5 volume % of a polymer additive comprising a poly(dialkyl-siloxane) segment chemically bonded to a polyurethane segment, the polymer additive being dispersed throughout the base polymer and being characterized by a γ_c less than that of the base polymer, the polymer mixture being characterized by a γ_c between 10 and 35 dyne/cm.

In a second aspect there is provided a method of forming a blood-compatible polymer mixture comprising the steps of

(a) throughly dispersing no greater than 5 volume % of a polymer additive throughout at least 95 volume % of a base polymer to form a polymer mixture, the polymer additive comprising a poly (dialkylsiloxane) segment component chemically bonded to a polyurethane segment, the polymer additive being characterized by a γ_c less than that of the base polymer and the polymer mixture being characterized by a γ_c between 10 and 35 dyne/cm.; and

(b) solidifying the polymer mixture.

The polymer mixture of the invention may be used to provide a technique for lowering the surface free energy of a good structural polymer to convert a surface formed from such material from one which is blood incompatible to one which is blood compatible. As used herein, the term "base polymer" will refer to the polymer whose surface characteristics is so modified. Typical base polymers whose surfaces may be improved by the present technique including polyurethanes, polysulfones, polycarbonates, polyesters, polyethylene, polypropylene, polystyrene, poly(acrylonitrile-butadiene-styrene), polybutadiene, polyisoprene, styrene-butadiene-styren block copolymers, styrene-isoprene-styrene block copolymers, poly-4-methylpentene, polyisobutylene, polymethyl-methacrylate, polyvinylacetat , polyacrylonitrile, polyvinyl chloride, polyethylene terephthalate, cellulose and its esters and derivatives, and the like.

The base polymer is of a type capable of being formed into a self-supporting structural body, a self-supporting film, or deposited as a coating onto a self-supporting body. The end use of the final product may be the surface of a biomedical device or component thereof.

Another characteristic of the base polymer is that it includes a critical surface tension (γ_c) in excess of that desirable for a blood contact surface and in excess of that of the polymer additive to be described below which reduces its γ_c value. As defined herein, γ_c measurements are performed by the direct method using a contact angle meter of the Kernc r Rame-Hart type and series of seven solvents acc rding to the Zisman procedure as set forth in A.W. Adamson, *Physical Chemistry for Surfaces* 339-357, 351 (3d Ed.). Measurements are made at room temperature using advancing angles on solvent cast films annealed at 60°C for four hours. The mean contact angles are fitted to a Zisman plot using a linear regression calculator program.

A base polymer of the foregoing type is mixed with a polymer additive as set out below to low r its surface free energy. The polymer additive with a substantially lower γ_c value than that f the base p lymer is th roughly dispers d into the base polymer while in fluid form to form a fluid polymer admixture. Thereafter, the polymer admixture is s lidified and generally formed into the blood-c ntacting surface f a bi medical d vice or component. The surfac fre energy f the polymer mixture is from 10 to 35 dyne/cm. while a pr f rred rang is

from 20 to 30 dyne/cm. An optimum range is 20-25 dyne/cm.

The polymer additive includes a poly(dialkylsiloxane) segment chemically bonded to a polyurethane segment. The poly(dialkylsiloxane) has a relatively low γ_c value, less than that of both the base polymer and the polyurethane and causes reduction in the γ_c of the polymer mixture as set out below.

The unique mixture according to the present invention includes a block or graft copolymer of poly(dialkylsiloxane), specifically poly(dimethylsiloxane), as the first component and polyurethane as the second component. As used herein, the term "polyurethane" encompasses polyetherurethaneureas, polyether urethanes, polyester urethanes, or any of the other known polyurethanes, e.g., as set forth in Nyilas U.S. Patent 3,562,352 (Col.2, line 66-Col. 3, line 37). This copolymer may be blended with any base polymer of desired physical properties. It is particularly effective for us with the same type of base polymer as the second component to provide improved compatibility.

Typically the poly(dialkylsiloxane) has a tendency to exude from the base polymer when in a mixture therewith and the polyurethane is chemically bonded to the poly(dialkysiloxane) in the polymer additive to lower this tendency to exude. For biomedical applications, the polyurethane is characterized by a crystalline melting point greater than about 37°C and/or a glass transition temperature also greater than about 37°C. The polyurethane has a higher surface free energy than the poly(dialkylsiloxane). For compatibility, the polyurethane is preferably also used as the base copolymer.

It has been found that the homopolymer component of the additive with the lower γ_c value controls the γ_c value of the entire polymer additive. Thus, for example, if the poly(dialkylsiloxane) has a γ_c value of 25 and the polyurethane a γ_c value of 35, the total γ_c of the annealed additive is approximately 25.

Suitable homopolymers for the poly(dialkylsiloxane) are those with a γ_c value in the desired range to lower the value of the base polymer to that desired for blood compatibility. Thus, it is preferable that the poly (dialkylsiloxane) be characterized by a γ_c value less than 30 dyne/cm. One particularly effective homopolymer for this purpose is a polydimethylsiloxane with a γ_c on the order of 22 dyne/cm. Techniques for forming siloxane copolymers for use in the present invention are known, e.g., as described in W. Noll, *Chemistry and Technology of Silicones* (Academic Press, 1968).

Where the polymer mixture of the present invention is formed by mixing a preformed polymer additive of the foregoing type with base polymer, such polymer additive is suitably formed of block copolymers of alternating first and second components interlinked by chemical bonds in accordance with known techniques. For example, such block copolymers may be formed as set out in A. Noshay and J.E. McGrath, Block Copolymers Overview and Critical Survey (Academic Press 1977). A suitable number of repeating units of poly(dialkylsiloxane) is that sufficient to retain the γ_c value of the poly(dialkylsiloxane) as evidenced by retention of approximately the same glass transition temperature as that of the pure poly(dialkylsiloxane). Typically, this number is on the order of 5 to 10 units or more. Similarly, there should be a sufficient number of repeating units of the polyurethane in a segment so that the polymer additive is solid at room temperature.

The preparation of block copolymers (or multipolymers) may be performed by several procedures which differ in the degree to which the structure f the resulting product may defined.

One procedure involves the coupling of two (r more) preformed blocks which are prepared in separate reactions prior to the coupling reaction. This procedure involves a very well defined structure if the coupling reaction precludes like blocks from reacting with themselves but only allows dissimilar blocks to couple to one another

A slightly less well defined structure results if the two preformed blocks posses the ability (via the coupling reaction) to react with themselves as well as with the dissimilar block.

An even less well defined structure results when a single (or more) preformed block is coupled with a second block created during the coupling reaction. In this case the initial length of the preformed block is known (by virtue of the separate reaction used to prepare it) but the sequence distribution of the copolymer is not known exactly since both coupling and chain growth is possible in the reaction which produces the second block. Suitable methods of forming these and other copolymers for use in the present invention are set out in the aforementioned Noshay and McGrath publication.

If desired, three or more types of polymer chains may be employed in sequence so long as at least one type has a low γ_c value. An excellent terpolymer additive includes a block copolymer segment of the poly(dialkylsiloxane) and and polyurethane. The polyurethane is linked to a segment formed of specifically either polyethylene oxide or polyethylene oxide-copolypropylene oxide, herein the "hydrophilic component". In this instance, the polyurethane is a hard block with a crystalline melting point above 37°C or a glass transition temperature above 37°C. In a terpolymer of this typ , the polyurethane links the poly(dialkylsiloxane) and the hydrophilic component. This terpolymer provides unexpectedly superior improvement in blood compatibility for a base polymer of the desired structural characteristic, such as a hard polymer of the same type as the polyurethane.

Other forms of linked first and second homopolymers are of the graft copolymer type. Either the poly(dialkylsiloxane) or the polyurethane may serve as the substrate upon which the pendant chains of the other type of homopolymer are grafted. The mode of forming graft copolymers is well knwon to those skilled in the polymer field. For example, se pp. 13-23 of the aforementioned Noshay and McGrath publication. The third mechanism in Tabl 2-1 illustrates a backbone structure suitable for grafting a hydroxyalkyl-terminated polydimethylsiloxane (e.g., through a urethane linkage using a diisocyanate)

The ratio of poly(dialkylsiloxane) to polyurethane in the polymer additive may vary to a considerable extend so long as there is sufficient amount of the poly(dialkylsiloxane) to reduce the γ_c value and sufficient amount of the polyurethane to prevent exudation of the polymer additive. It is preferable that the polymer additive include at least about 20 volume % of the poly (dialkylsiloxane). A suitable ratio is from 20 to 80 volume % of the poly(dialkylsiloxane) and about 20 to 80 volume % of the polyurethane.

The total amount of polymer additive required to reduce the γ_c value of the base polymer to that desired for the polymer mixture is very low. Thus, it has been found that less than 5 volume % and preferably less than 1 to 2 volume % of the total polymer additive performs this function even though the first component typically comprises about half or less of the polymer additive. A suitable ratio of polymer additive to base polymers is on the order of 0.00002 to 2 volume % polymer additive based on the total polymer mixture. Experimental results have indicated that even though the polymer additive is initially mixed in bulk into the base polymer, it migrates to the surface to form an exceptionally thin (monomolecular) film which provides the desired surface characteristics. Sufficient polymer additive should be included to provide this uniform layer. The presence of an adequate amount of polymer additive is shown by a dramatic drop in the γ_c value of the polymer mixture to approximately that of the first component. While the required amount varies from system to system, it is generally less than 1 volume % of the first component based on the total polymer mixture. It is advantageous to use such low amounts of polymer additive as large amounts of the first component can be detrimental to the physical properties of the polymer mixture.

It has been found that the required minimum amount of polymer additive may be approximated by a knowledge of the film thickness of a polymer additive monolayer and the surface area to bulk volume ratio of the fabricated material. This is based on the simplifying assumption that prior to surface saturation, essentially all of the polymer additive migrates to the surface. By simple calculation, this minimum amount may be precalculated based on this knowledge.

A number of techniques may be employed for mixing the polymer additive with the base polymer in accordance with the present invention. In one technique, both the base polymer and polymer additive are thermoplastic and are melted at elevated temperatures to perform the mixing. Thereafter, the polymer is solidified by cooling. If desired, the bulk polymer may be simultaneously processed into the desired final form. Alternatively, the material may be solidified for subsequent formation of the material into the desired form by thermoplastic methods such as injection moulding and extrusion.

Another technique for mixing of the polymer additive and base polymer is by dissolving both f them in solvent and thereaft r vaporating the solvent to form the solid product of the present invention. This product may also be subsequently processed by thermoplastic techniques if desired.

A third technique for forming the polymer mixture of the present invention is to polymerize in place with a vast excess (at least 95 volume %) of base polymer and a minor amount (no greater than 5 volume %) of a homopolymer additive of the first component type set out above. For example, low molecular weight polydimethylsiloxane having hydroxypropyl end groups is substituted for a small amount of polyetherglycol in the synthesis of a typical polyether urethane. Here the reaction product can contain enough silicone/polyurethane block copolymer to provide the desired surface characteristics. The concentration of the polymer additive would be so low that the great majority (at least 95 volume %) of the base polymer would not be linked to the additive polymer.

The polymer additive of the present invention must be thoroughly dispersed in the base polymer. For this purpose, it is preferable that the polymer additive be thermoplastic, soluble in organic solvents, and relatively uncrosslinked.

For most biomedical applications, the base polymers of the present invention should be thermoplastic so that they may be readily processed as desired. However, there are certain applications in which the polymers may be fabricated while fluid and thereafter solidified in the form of the fabricated part which cannot again be placed into the fluid form. For example, such base polymer may comprise thermosetting systems which are cured or vulcanized immediately following dispersion of the polymer additive. Such systems may include two component polyurethanes or epoxy resin systems.

A particularly effective mixture includes a polymer additive comprising a block copolymer of about 50 weight % polydimethylsiloxane and 50 weight % polyurethane (specifically polyesterurethane) in a base polymer of polyurethane (specifically polyesterurethane). A suitable ratio is 99.9% polyester urethane based polymer and 0.1% of the block copolymer.

One mode of pretreating a base polymer to lower its surface free energy is believed to be effectiv with a base polymer which includes high energy end groups, specifically ones capable of hydrogen b nding or reacting with protein. In this instance, the base polymer is first fractionated to remove a lower molecular weight fraction and thereby may reduce the hydrogen bonding capacity of the remaining base polymer. Suitable techniques for accomplishing this are set out in Manfred J.R. Cantow, *Polymer Fractionation*, Academic Press (New York - London 1967). Such techniques include liquid chr - matography, particularly gel permeation chromotography.

It has been found that variations in processing conditions which would otherwise affect the surfac free energy to a significant extent may be minimized as a factor in systems of the present invention by the use of a short heat treatment following surface formation. For example, in a system comprising a base polymer of polyether urethane and a block copolymer of p lyether urethane/polyalkylsiloxane, annealing for four hours at 75°C yields a γ_c value

approximately equal to that of pure polysiloxane while it takes a considerably longer period of time t accomplish this objective at room temperature.

It has further been found that the polarity of the environment of formation affects the γ_c value of the surface. Thus an air equilibrated surface provides a lower γ_c than one which has been equilibrated in water.

The polymer mixtures of the present invention are particularly effective for use as a blood-contacting surface of a biomedical device or component. Such devices include auxiliary ventricles, intra-aortic balloons, and various types of blood pumps.

A further disclosure of the nature of the present invention is provided by the following specific examples of the practice of the invention. It should be understood that the data disclosed serve only as examples and are not intended to limit the scope of the invention.

Example 1

A typical synthesis of Polydimethylsiloxane-Polyurethane Block Copolymer.

To a 500 ml. four-necked flask equipped with stirrer, Dean and Stark trap, dropping funnel, drying tube, thermometer and inert gas inlet is placed a mixture of 50 ml. dimethylformamide and 140 ml. of tetrahydrofuran. The mixture is heated to reflux and approximately 40 ml. tetrahydrofuran is distilled off. The reaction mixture is cooled down and 12.513 gm (0.05 mole) of methylene bis (4-phenyl) isocyanate (MDI) is added to give a clear solution. From the dropping funnel 15.000 gm (0.015 mole) of 3-hydroxypropyl terminated polydimethylsiloxane (Mol. wt≈ 1,000) is added dropwise. The reaction mixture is heated at 105-100°C for 1 hour, followed by dropwise addition of 3.15 gm (0.035 mole) of 1-4, butane diol over a period of 45 minutes. The polymerization is carried out for 15 minutes more, cooled down and precipitated by pouring into water in a blender. The slightly yellowish polymer is washed with water and finally with ethanol; dried in a vacuum oven at 50°C to afford ≈30-31 gm of polymer (98-100%). $[\eta]$ in tetrahydrofuran at 25°C is 0.19.

Example 2

By replacing some of the hydroxypropyl-terminated polydimethylsiloxane with polyethylene glycol, a polydimethylsiloxane/polyethylene oxide/polyurethane terpolymer is prepared.

Example 3

By replacing the DMF solvent with dimethylacetamide and substituting ethylene diamine for butane diol in Example 2 a polydimethylsiloxane/polyethylene oxide/polyureaurethane terpolym r is prepared.

Example 4

This example illustrates solution fabrication. A solution is prepared containing about 10 weight % mixture in a solvent system consisting of 90% tetrahydrofuran (vol/vol) and 10% dimethylformamide. The mixture consists of 99.9 weight % purifi d polyesterurethane and 0.1 weight % silicone/polyurethane block copolymer. The block copolymer consists of about 50 weight % polydimethylsiloxane and 50 weight % polyurethane from diphenylmethane diisocyanate and butane diol.

The solution is coated onto tapered stainless steel mandrels by multiple dipping. The solvent is allowed to evaporate and the film is removed from the mandrel. the resulting "balloon" is mounted on a pre-drilled catheter and is useful as a cardiac arrest device when placed in the descending aorta and inflated and deflated with CO_2 in counterpulsation to the heart.

The γ_c of the balloon film is 20 to 22 dyne/cm.

Example 5

Small test tubes are coated on their inner surface with two different polymer solutions (in THF) at 10 weight % concentration. One solution consists of polyetherurethane in the solvent. The second solution consists of 90 weight % solvent, 9.9 weight % polyetherurethane and 0.1 weight % copolymer additive. The copolymer consists of about 50% polydimethyl-siloxane and 50% polyethylene oxide co-polypropylene oxide available from Petrarch Systems under the trade registration PS 072.

After solvent evaporation and about 16 hours equilibration in distilled water, fresh whole blood is placed in three tubes of each type.

Tubes coated with the unmodified polyetherurethane give mean whole blood clotting times of 39 minutes. Tubes coated with polyetherurethane containing the block copolymer additive give mean whole blood clotting times greater than 70 minutes.

The γ_c of the unmodified polyetherurethane is about 28 dyne/cm. The γ_c of the polyetherurethane containing the block copolymer additive is about 20 dyne/cm.

Example 6

This example illustrates thermoplastic fabrication.

A thermoplastic polyurethane is mixed in a single screw extruder at about 400°F with a block copolymer additive consisting of about 50 weight % polydimethylsiloxane and 50 weight % polyetherurethane such that the total silicone concentration of the mixture is 0.01 weight %. The mixture is extruded into the shape of tubing suitable for th transfer of blood. The tubing has a γ_c of about 21 dyne/cm after being annealed at 60°C for six hours.

Example 7

This example illustrates two component vulcanizing.

DuPont Adiprene L-167 polyetherurethane isocyanate terminated prepolymer is prepared according to the manufactuer's recommendations for a polyol cure, using a slight stoichiometric deficiency of butane diol/trimethylol propane mixture. Whil still liquid 0.1 weight % of the block copolym r additive of Example 1 is mixed with the reactants and an amine catalyst.

The resulting mixture is coated on a previously primed titanium connector and cured in an oven at 100°C.

The coated connector has a γ_c of about 20 dyne/cm. and is used in contact with blood t connect a conduit to a left ventricular assist device which is used to treat low cardiac output syndrome.

Example 8

A 4 mm tubular prosthesis was formed by coating a stainless steel mandrel with a polymer mixture consisting of 99.9 weight % poly(etherurethane urea) and 0.2 weight % polydimethylsiloxane/ polyurethane block copolymer containing 50% polydimethylsiloxane, 50% polyurethane, in a dimethylacetamide solution. After solvent evaporation, the resulting tube was removed from the mandrel, extracted with distilled water at 60°C for 16 hours, dried and annealed for 4 hours at 60°C. After ethylene oxide sterilization the tube was sutured to the carotid artery of a goat.

Using an established radiolabeled platelet technique no enhancement in platelet turnover was measured relative to a sham experiment. A similar experiment easily detects changes on platelet turnover in polyvinylchloride tubing which is known to have low blood compatibility.

CLAIMS

1. A blood-compatible polymer mixture comprising at least 95 volume % of a base polymer and no greater than 5 volume % of a polymer additive comprising a poly (dialkylsiloxane) segment chemically bonded to a polyurethane segment, the polymer additive being dispersed throughout the base polymer and being characterized by a γ_c less than that of the base polymer, the polymer mixture being characterized by a γ_c between 10 and 35 dyne/cm.

2. A polymer mixture as claimed in Claim 1 in the form of the blood contacting surface of a biomedical device or component.

3. A polymer mixture as claimed in Claim 1 or Claim 2 in which the polymer additive is a graft copolymer.

4. A polymer mixture as claimed in Claim 1 or Claim 2 in which the polymer additive is a block copolymer.

5. A polymer mixture as claimed in any one of Claims 1 to 4 in which the base polymer is a polyurethane.

6. A polymer mixture as claimed in any one of the preceding claims wherein the poly(dialkylsiloxane) is poly(dimethylsiloxane).

7. A polymer mixture as claimed in any one of the preceding claims which comprises of from about 0.00002 to 2 volume % polymer additive based on the total polymer mixture.

8. A polymer mixture as claimed in any one of the preceding claims in which the polymer additive comprises at least 20 volume % of the poly(dialkylsiloxane).

9. A polymer mixture as claimed in Claim 8 in which the polymer additive comprises 20 to 80 volume % of the poly(dialkylsiloxane) and 20 to 80 volume % of the polyurethane.

10. A method of forming a blood-compatible polymer mixture comprising the steps f

(a) throughly dispersing no greater than 5 volume % of a polymer additive throughout at least 95 volume % of a base polymer to form a polymer mixture, the polymer additive comprising a poly-(dialkylsiloxane) segment component chemically bonded to a polyurethane segment, the polym r additive being characterized by a γ_c less than that of the base polymer and the polymer mixture being characterized by a γ_c between 10 and 35 dyne/cm.; and

(b) solidifying the polymer mixture.

11. A method as claimed in Claim 10 in which the poly(dialkylsiloxane) is poly(dimethylsiloxane).

12. A method as claimed in Claim 10 or Claim 11 in which the base polymer is a polyurethane.

13. A method as claimed in any one of Claims 10 to 12 in which about 0.00002 to 2 volume % polym r additive is added to the base polymer based on th total polymer mixture.

14. A method as claimed in any one of Claims 10 to 13 in which the polymer additive comprises at least 20 volume % of the poly(dialkylsiloxane).

15. A method as claimed in Claim 15 in which the polymer additive comprises 20 to 80 volume % of the poly(dialkylsiloxane) and 20 to 80 volume % of the polyurethane.

16. A polymer mixture as claimed in claim 1 substantially as hereinbefore described.

17. A method of forming a blood-compatibl polymer mixture as claimed in claim 10 substantially as hereinbefore described.

Amendments to the claims have been filed and have the following effect:-

New or textually amended claims have been filed as follows:-

7. A polymer mixture as claimed in any one of the preceding claims which comprises of from 0.00002 to 2 volume % polymer additive based on the total polymer mixture.

13. A method as claimed in any one of Claims 10 to 12 in which 0.00002 to 2 volume % polymer additive is added to the base polymer based on the total polymer mixture.

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